VICTOZA® (liraglutide) injection, for subcutaneous use

**INDICATIONS AND USAGE**

VICTOZA® is a glucagon−like peptide−1 (GLP−1) receptor agonist indicated:

• as an adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus (1).

• to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus (1).

**Limitations of Use:**

• Not for treatment of type 1 diabetes mellitus.

• Should not be coadministered with other liraglutide-containing products.

**ADVERSE REACTIONS**

Injection site reactions are the most common adverse reaction:

• Injection site reactions (6.1).

**CONTRAINDICATIONS**

VICTOZA® is contraindicated in patients with a prior serious hypersensitivity reaction to liraglutide or any of the excipients in VICTOZA® (4).

**WARNINGS AND PRECAUTIONS**

- Thyroid C-cell Tumors: See Boxed Warning (5.1).

- Pancreatitis: Postmarketing reports, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed (5.2).

- Never share a VICTOZA® pen between patients, even if the needle is changed (5.3).

- Hypoglycemia: Adult patients taking an insulin secretagogue or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with VICTOZA® regardless of insulin and/or metformin use. Reduction in the dose of insulin secretagogues or insulin may be necessary (5.4).

- Renal Impairment: Postmarketing, usually in association with nausea, vomiting, diarrhea, or dehydration which may sometimes require hemodialysis. Use caution when initiating or escalating doses of VICTOZA® in patients with renal impairment (5.5).

- Hypersensitivity: Postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema). Discontinue VICTOZA® and promptly seek medical advice (5.6).

- Acute Gallbladder Disease: If cholelithiasis or cholecystitis are suspected, gallbladder studies are indicated (5.7).

**ADVERSE REACTIONS**

- The most common adverse reactions, reported in ≥5% of patients treated with VICTOZA® are:
  - nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation (6.1).
  - Immunogenicity-related events, including urticaria, were more common among VICTOZA®-treated patients (0.8%) than among comparator-treated patients (0.4%) in clinical trials (6.2).

To report SUSPECTED ADVERSE REACTIONS, contact Novo Nordisk Inc. at 1−877−484−2869 or FDA at 1−800−FDA−1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

- Oral Medications: VICTOZA® delays gastric emptying and may impact absorption of concomitantly administered oral medications (7).

- Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin: When initiating, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia (7).

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (8.1).

See 17 for PATIENT COUNSELING INFORMATION and FDA-Approved Medication Guide.

**RECENT MAJOR CHANGES**

Indications and Usage, Limitations of Use (1) Removed 11/2020

Warnings and Precautions (5.4) Removed 11/2020
VICTOZA® (liraglutide) injection 1.2 mg, 1.8 mg

Cases of MTC in patients treated with VICTOZA® have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and VICTOZA® use in humans.

VICTOZA® is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of VICTOZA® and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with VICTOZA® [see Contraindications (4) and Warnings and Precautions (5.1)].

5.2 Pancreatitis

Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with VICTOZA®. After initiation of VICTOZA®, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, VICTOZA® should promptly be discontinued and appropriate management should be initiated. If pancreatitis is confirmed, VICTOZA® should not be restarted.

In glycemic control trials of VICTOZA®, there have been 13 cases of pancreatitis among VICTOZA®-treated patients and 1 case in a comparator (glimepiride) treated patient (2.7 vs. 0.5 cases per 1000 patient-years). Nine of the 13 cases with VICTOZA® were reported as acute pancreatitis and four were reported as chronic pancreatitis. In one case in a VICTOZA®-treated patient, pancreatitis, with necrosis, was observed and led to death; however clinical causality could not be established. Some patients had other risk factors for pancreatitis, such as a history of cholelithiasis or alcohol abuse.

VICTOZA® has been studied in a limited number of patients with a history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on VICTOZA®.

5.3 Never Share a VICTOZA® Pen Between Patients

VICTOZA® pens must never be shared between patients, even if the needle is changed. Pen-sharing poses a risk for transmission of blood-borne pathogens.

5.4 Hypoglycemia

Adult patients receiving VICTOZA® in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia. In pediatric patients 10 years of age and older, the risk of hypoglycemia was higher with VICTOZA® regardless of insulin and/or metformin use [see Adverse Reactions (6.1), Drug Interactions (7.2)].

The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogues) or insulin. Inform patients using these concomitant medications and pediatric patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

5.5 Renal Impairment

VICTOZA® has not been found to be directly nephrotoxic in animal studies or clinical trials. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis in VICTOZA®-treated patients [see Adverse Reactions (6.2)]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration [see Adverse Reactions (6.1)]. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA®. Use caution when initiating or escalating doses of VICTOZA® in patients with renal impairment [see Use in Specific Populations (8.6)].

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylactic reactions and angioedema) in patients treated with VICTOZA®. If a hypersensitivity reaction occurs, discontinue VICTOZA®, treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous hypersensitivity reaction to VICTOZA® [see Contraindications (4)]. Anaphylaxis and angioedema have been reported with other GLP-1 receptor agonists. Use caution in a patient with a history of anaphylaxis or angioedema with another GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with VICTOZA®.

5.7 Acute Gallbladder Disease

In the LEADER trial [see Clinical Studies (14.3)], 3.1% of VICTOZA®-treated patients versus 1.9% of placebo-treated patients reported an acute event of gallbladder disease, such as cholecystitis or cholecystolithiasis. The majority of events required hospitalization or cholecystectomy. If cholecystitis is suspected, gallbladder studies and appropriate clinical follow-up are indicated.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors [see Warnings and Precautions (5.1)]
- Pancreatitis [see Warnings and Precautions (5.2)]
- Hypoglycemia [see Warnings and Precautions (5.4)]
- Renal Impairment [see Warnings and Precautions (5.5)]
- Hypersensitivity Reactions [see Warnings and Precautions (5.6)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
Common Adverse Reactions

The safety of VICTOZA® in subjects with type 2 diabetes was evaluated in 5 glycemic control, placebo-controlled trials in adults and one trial of 52 weeks duration in pediatric patients 10 years of age and older (see Clinical Studies (14.1)). The data in Table 1 reflect exposure of 1673 adult patients to VICTOZA® and a mean duration of exposure to VICTOZA® of 37.3 weeks. The mean age of adult patients was 58 years, 4% were 75 years or older and 54% were Female. The population was 73% White, 6% Black or African American, 13% Asian; 4% were of Hispanic or Latino ethnicity. At baseline the population had diabetes for an average of 9.1 years and a mean HbA1c of 8.4%. Baseline estimated renal function was normal or mildly impaired in 88.1% and moderately impaired in 11.9% of the pooled population.

Table 1 shows common adverse reactions in adults, excluding hypoglycemia, associated with the use of VICTOZA®. These adverse reactions occurred more commonly on VICTOZA® than on placebo and occurred in at least 5% of patients treated with VICTOZA®. Overall, the type and severity of adverse reactions in adolescents and children aged 10 years and above were comparable to that observed in the adult population.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Placebo N = 661</th>
<th>Liraglutide 1.2 mg N = 645</th>
<th>Liraglutide 1.8 mg N = 1024</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5 (0.76)</td>
<td>10 (1.6)</td>
<td>18 (1.7)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (0.61)</td>
<td>9 (1.4)</td>
<td>12 (1.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (1.1)</td>
<td>11 (1.7)</td>
<td>10 (1.0)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (1.2)</td>
<td>9 (1.4)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (0.3)</td>
<td>6 (0.9)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1 (0.02)</td>
<td>10 (1.6)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (0.02)</td>
<td>4 (0.6)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>6 (0.9)</td>
<td>6 (1.0)</td>
<td>6 (0.6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (0.02)</td>
<td>5 (0.8)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>Back Pain</td>
<td>3 (0.4)</td>
<td>4 (0.6)</td>
<td>5 (0.5)</td>
</tr>
</tbody>
</table>

Cumulative proportions were calculated combining studies using Cochran-Mantel-Haenszel weights.

In an analysis of placebo- and active-controlled trials, the types and frequency of common adverse reactions, excluding hypoglycemia, were similar to those listed in Table 1.

Other Adverse Reactions

Gastrointestinal Adverse Reactions

In the pool of 5 glycemic control, placebo-controlled clinical trials, withdrawals due to gastrointestinal adverse reactions, occurred in 4.3% of VICTOZA®-treated patients and 0.5% of placebo-treated patients. Withdrawal due to gastrointestinal adverse events mainly occurred during the first 2-3 months of the trials.

Injection site reactions

Injection site reactions (e.g., injection site rash, erythema) were reported in approximately 2% of VICTOZA®-treated patients in the five double-blind, glycemic control trials of at least 26 weeks duration. Less than 0.2% of VICTOZA®-treated patients discontinued due to injection site reactions.

Hypoglycemia

In 5 adult glycemic control, placebo-controlled clinical trials of at least 26 weeks duration, hypoglycemia requiring the assistance of another person for treatment occurred in 8 VICTOZA®-treated patients (7.5 events per 1000 patient-years). Of these 8 VICTOZA®-treated patients, 7 patients were concomitantly using a sulfonylurea.

6.2 Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmacueticals, patients treated with VICTOZA® may develop anti-liraglutide antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to liraglutide cannot be directly compared with the incidence of antibodies to other products.

Approximately 50-70% of VICTOZA®-treated patients in five double-blind clinical trials of 26 weeks duration or longer were tested for the presence of anti-liraglutide antibodies at the end of treatment. Low titers (concentrations not requiring dilution of serum) of anti-liraglutide antibodies were detected in 8.6% of these VICTOZA®-treated patients. Cross-reacting anti-liraglutide antibodies to native glucagon-like peptide-1 (GLP-1) occurred in 6.9% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 4.8% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials. These cross-reacting antibodies were not tested for neutralizing effect against native GLP-1, and thus the potential for clinically significant neutralization of native GLP-1 was not assessed. Antibodies that had a neutralizing effect on liraglutide in an in vitro assay occurred in 2.3% of the VICTOZA®-treated patients in the double-blind 52-week monotherapy trial and in 1.0% of the VICTOZA®-treated patients in the double-blind 26-week add-on combination therapy trials.

Antibody formation was not associated with reduced efficacy of VICTOZA® when comparing mean HbA1c of all antibody-positive and all antibody-negative patients. However, the 3 patients with the highest titers of anti-liraglutide antibodies had no reduction in HbA1c with VICTOZA® treatment.

In five double-blind glycemic control trials of VICTOZA®, events from a composite of adverse events potentially related to immunogenicity (e.g., urticaria, angioedema) occurred among 0.8% of VICTOZA®-treated patients and among 0.4% of comparator-treated patients. Urticaria accounted for approximately one-half of the events in this composite for comparator-treated patients. Patients who developed anti-liraglutide antibodies were not more likely to develop events from the immunogenicity composite than were patients who did not develop anti-liraglutide antibodies.

In the LEADER trial [see Clinical Studies (14.3)], anti-liraglutide antibodies were detected in 11 out of the 1247 (0.9%) VICTOZA®-treated patients with antibody measurements.

Of the 11 VICTOZA®-treated patients who developed anti-liraglutide antibodies, none were observed to develop neutralizing antibodies to liraglutide, and 5 patients (0.4%) developed cross-reacting antibodies against native GLP-1.
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In a clinical trial with pediatric patients 10 to 17 years [see Clinical Studies (14.2)], anti-liraglutide antibodies were detected in 1 (1.5%) VICTOZA® treated patient at week 26 and 5 (8.5%) VICTOZA® treated patients at week 53. None of the 5 had antibodies cross reactive to native GLP-1 or had neutralizing antibodies.

6.3 Post-Marketing Experience

The following additional adverse reactions have been reported during post-approval use of VICTOZA®. Because these events are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Medullary thyroid carcinoma
- Dehydration resulting from nausea, vomiting and diarrhea.
- Increased serum creatinine, acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis.
- Angiodema and anaphylactic reactions.
- Allergic reactions: rash and pruritus.
- Acute pancreatitis, hemorrhagic and necrotizing pancreatitis sometimes resulting in death.

7 DRUG INTERACTIONS

7.1 Oral Medications

VICTOZA® causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA® did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA®.

7.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin

When initiating VICTOZA®, consider reducing the dose of concomitantly administered insulin secretagogues (such as sulfonylureas) or insulin to reduce the risk of hypoglycemia [see Warnings and Precautions (5.4) and Adverse Reactions (6)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA® during pregnancy. VICTOZA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal reproduction studies identified increased adverse developmental outcomes from exposure during pregnancy. Liraglutide exposure was associated with early embryonic deaths and an imbalance in some fetal abnormalities in pregnant rats administered liraglutide during organogenesis at doses that approximate clinical exposures at the maximum recommended human dose (MRHD) of 1.8 mg/day. In pregnant rabbits administered liraglutide during organogenesis, decreased fetal weight and an increased incidence of major fetal abnormalities were seen at exposures below the human exposures at the MRHD [see Animal Data].

The estimated background risk of major birth defects for women with uncontrolled pre-gestational diabetes (Hemoglobin A1c >7) is 6% to 10%. The major birth defect rate has been reported to be as high as 20 to 25% in women with a Hemoglobin A1c >10. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% - 4% and 15%-20%, respectively.

Clinical Considerations

- Disease-associated maternal and/or embryo/fetal risk
- Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia related morbidity.

Animal Data

Female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide beginning 2 weeks before mating through gestation day 17 had estimated systemic exposures 0.8-, 3-, and 11-times the human exposure at the MRHD based on plasma AUC comparison. The number of early embryonic deaths in the 1 mg/kg/day group increased slightly. Fetal abnormalities and variations in kidneys and blood vessels, irregular ossification of the skull, and a more complete state of ossification occurred at all doses. Mottled liver and minimally kinked ribs occurred at the highest dose. The incidence of fetal malformations in liraglutide-treated groups exceeding concurrent and historical controls were missiphan orpharynx and/or narrowed opening into larynx at 0.1 mg/kg/day and umbilical hernia at 0.1 and 0.25 mg/kg/day.

Pregnant rabbits given subcutaneous doses of 0.01, 0.025 and 0.05 mg/kg/day liraglutide from gestation day 6 through day 18 inclusive, had estimated systemic exposures less than the human exposure at the MRHD of 1.8 mg/day at all doses, based on plasma AUC. Liraglutide decreased fetal weight and dose-dependently increased the incidence of total major fetal abnormalities at all doses. The incidence of malformations exceeded concurrent and historical controls at 0.01 mg/kg/day (kidneys, scapula), > 0.01 mg/kg/day (eyes, forelimb), 0.025 mg/kg/day (brain, tail and sacral vertebrae, major blood vessels and heart, umbilicus), > 0.025 mg/kg/day (sternum) and at 0.05 mg/kg/day (parietal bones, major blood vessels). Irregular ossification and/or skeletal abnormalities occurred in the skull and jaw, vertebræ and ribs, sternum, pelvis, tail, and scapula; and dose-dependent minor skeletal variations were observed. Visceral abnormalities occurred in blood vessels, lung, liver, and esophagus. Bilobed or bifurcated gallbladder was seen in all treatment groups, but not in the control group.

In pregnant female rats given subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide from gestation day 6 through weaning or termination of nursing on lactation day 24, estimated systemic exposures were 0.8-, 3-, and 11-times human exposure at the MRHD of 1.8 mg/day, based on plasma AUC. A slight delay in parturition was observed in the majority of treated rats. Group mean body weight of neonatal rats from liraglutide-treated dams was lower than neonatal rats from control group dams. Bloody scabs and agitated behavior occurred in male rats descended from dams treated with 1 mg/kg/day liraglutide. Group mean body weight from birth to postpartum day 14 trended lower in F2 generation rats descended from liraglutide-treated rats compared to F2 generation rats descended from controls, but differences did not reach statistical significance for any group.

8.2 Lactation

Risk Summary

There are no data on the presence of VICTOZA® in human milk, the effects on the breastfed infant, or the effects on milk production. Liraglutide was present in milk of lactating rats [see Data].

Developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for VICTOZA® and any potential adverse effects on the breastfed infant from VICTOZA® or from the underlying maternal condition.

Data

In lactating rats, liraglutide was present unchanged in milk at concentrations approximately 50% of maternal plasma concentrations.

8.4 Pediatric Use

The safety and effectiveness of VICTOZA® as an adjunct to diet and exercise to improve glycemic control in type 2 diabetes mellitus have been established in pediatric patients 10 years of age and older.

Use of VICTOZA® for this indication is supported by a 26-week placebo-controlled clinical trial and a 26-week open-label extension in 134 pediatric patients 10 to 17 years of age with type 2 diabetes, a pediatric pharmacokinetic study, and studies in adults with type 2 diabetes mellitus [see Clinical Pharmacology (12.3) and Clinical Studies (14.1,14.2)]. The risk of hypoglycemia was higher with VICTOZA® in pediatric patients regardless of insulin and/or metformin use.

The safety and effectiveness of VICTOZA® have not been established in pediatric patients less than 10 years of age.

8.5 Geriatric Use

In the VICTOZA® treatment arms of the glycemic control trials, a total of 832 (19.3%) of the patients were 65 to 74 years of age and 145 (3.4%) were 75 years of age and over. No overall differences in safety or efficacy were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

In the VICTOZA® treatment arm of the LEADER trial [see Clinical Studies (14.3)], a total of 1738 (37.2%) patients were 65 to 74 years of age, 401 (8.6%) were 75 to 84 years of age, and 17 (0.4%) were 85 years of age or older at baseline. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

No dose adjustment of VICTOZA® is recommended for patients with renal impairment [see Clinical Pharmacology (12.3)]. The safety and efficacy of VICTOZA® was evaluated in a 26-week clinical study that included patients with moderate renal impairment (eGFR 30 to 60 mL/min/1.73m²) [see Clinical Studies (14.1)].

In the VICTOZA® treatment arm of the LEADER trial [see Clinical Studies (14.3)], 1932 (41.4%) patients had mild renal impairment, 999 (21.4%) patients had moderate renal impairment and 117 (2.5%) patients had severe renal impairment at baseline. No overall differences in safety or efficacy were seen in these patients compared to patients with normal renal function.

There is limited experience with VICTOZA® in patients with end stage renal disease. There have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis [see Warnings and Precautions (5.5) and Adverse Reactions (6.2)]. Use caution in patients who experience dehydration.

8.7 Hepatic Impairment

There is limited experience in patients with mild, moderate or severe hepatic impairment. Therefore, VICTOZA® should be used with caution in this patient population. No dose adjustment of VICTOZA® is recommended for patients with hepatic impairment [see Clinical Pharmacology (12.3)].

8.8 Gastropareis

VICTOZA® slows gastric emptying. VICTOZA® has not been studied in patients with pre-existing gastroparesis.

10 OVERDOSE

Overdoses have been reported in clinical trials and post-marketing use of VICTOZA®. Observed effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient’s clinical signs and symptoms.

11 DESCRIPTION

VICTOZA® contains liraglutide, an analog of human GLP-1 and acts as a GLP-1 receptor agonist. The peptide precursor of liraglutide, produced by a process that includes expression of recombinant DNA in Saccharomyces cerevisiae, has been engineered to be 97% homologous to native human GLP-1 by substituting arginine for lysine at position 34. Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor. The molecular formula of liraglutide is C127H228N46O70S and the molecular weight is 3751.2 Dalton. The structural formula (Figure 1) is:

Figure 1 Structural Formula of liraglutide
12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action
Liraglutide is an analog of human Glucagon-Like Peptide-1 (GLP-1). GLP-1 receptor agonists with 97% amino acid sequence homology to endogenous human GLP-1 (7-37) GLP-1 (7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1 (7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

GLP-1 (7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

12.2 Pharmacodynamics
VICTOZA’s pharmacodynamic profile is consistent with its pharmacokinetic profile observed after single subcutaneous administration as VICTOZA lowered fasting, premeal and postprandial glucose throughout the day (see Clinical Pharmacology (12.3)).

Fasting and postprandial glucose was measured before and up to 5 hours after a standardized meal after treatment to steady state with 0.6, 1.2 and 1.8 mg VICTOZA or placebo. Compared to placebo, the postprandial plasma glucose AUC(0-∞) was 35% lower after VICTOZA 1.2 mg and 38% lower after VICTOZA 1.8 mg.

Glucose-dependent insulin secretion
The effect of a single dose of 7.5 mg/kg (~0.7 mg) VICTOZA on insulin secretion rates (ISR) was investigated in 10 patients with type 2 diabetes during graded glucose infusion. In these patients, on average, the ISR response was increased in a glucose-dependent manner (Figure 2).

Figure 2: Mean Insulin Secretion Rate (ISR) versus Glucose Concentration Following Single-Dose VICTOZA 7.5 mg/kg (~0.7 mg) or Placebo in Patients with Type 2 Diabetes (N=10) During Graded Glucose Infusion

Glucagon secretion
VICTOZA lowered blood glucose by stimulating insulin secretion and lowering glucagon secretion. A single dose of VICTOZA 7.5 mg/kg (~0.7 mg) did not impair glucagon response to low glucose concentrations.

Gastric emptying
VICTOZA causes a delay of gastric emptying, thereby reducing the rate at which postprandial glucose appears in the circulation.

Cardiac Electrophysiology (QTc)
The effect of VICTOZA on cardiac repolarization was tested in a QTc study. VICTOZA at steady state concentrations with daily doses up to 1.8 mg did not produce QTc prolongation.

12.3 Pharmacokinetics
Absorption - Following subcutaneous administration, maximum concentrations of liraglutide are achieved at 8-12 hours post dosing. The mean peak (C_max) and total (AUC) exposures of liraglutide were 35 ng/mL and 960 ng·h/mL, respectively, for a subcutaneous single dose of 0.6 mg. After subcutaneous single dose administrations, C_max and AUC of liraglutide increased proportionally over the therapeutic dose range of 0.6 mg to 1.8 mg. At 1.8 mg VICTOZA, the average steady state concentration of liraglutide over 24 hours was approximately 128 ng/mL. AUC(0-∞) was equivalent between upper arm and abdomen, and between upper arm and thigh. AUC(0-∞) from thigh was 22% lower than that from abdomen. However, liraglutide exposures were considered comparable among these three subcutaneous injection sites. Absolute bioavailability of liraglutide following subcutaneous administration is approximately 55%.

Distribution - The mean apparent volume of distribution after subcutaneous administration of VICTOZA 0.6 mg is approximately 13 L. The mean volume of distribution after intravenous administration of VICTOZA is 0.07 L/kg. Liraglutide is extensively bound to plasma protein (~98%).
13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
A 104-week carcinogenicity study was conducted in male and female Sprague Dawley rats at doses of 0.075, 0.25 and 0.75 mg/kg/day liraglutide administered by bolus subcutaneous injection with exposures 0.5-, 2- and 8-times the human exposure, respectively, resulting from the MRHD based on plasma AUC comparison. A treatment-related increase in benign thyroid C-cell adenomas was observed in males at 0.25 and 0.75 mg/kg/day liraglutide groups with incidences of 12%, 16%, 42%, and 46% and in all female liraglutide-treated groups with incidences of 10%, 27%, 33%, and 56% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. A treatment-related increase in malignant thyroid C-cell carcinomas was observed in all male liraglutide-treated groups with incidences of 2%, 8%, 6%, and 14% and in females at 0.25 and 0.75 mg/kg/day with incidences of 0%, 0%, 4%, and 6% in 0 (control), 0.075, 0.25, and 0.75 mg/kg/day groups, respectively. Thyroid C-cell carcinomas are rare findings during carcinogenicity testing in rats. Studies in mice demonstrated that liraglutide-induced C-cell proliferation was dependent on the GLP-1 receptor and that liraglutide did not cause activation of the REarranged during Transfection (RET) proto-oncogene in thyroid C-cells.

Human relevance of thyroid C-cell tumors in mice and rats is unknown and has not been determined by clinical studies or nonclinical studies. See Boxed Warning and Warnings and Precautions (S.1)). Liraglutide was negative with and without metabolic activation in the Ames test for mutagenicity and in a human peripheral blood lymphocyte chromosome aberration test for clastogenicity. Liraglutide was negative in repeat-dose in vivo micronucleus tests in rats. In rat fertility studies using subcutaneous doses of 0.1, 0.25 and 1.0 mg/kg/day liraglutide, males were treated for 4 weeks prior to and throughout mating and females were treated 2 weeks prior to and throughout mating until gestation day 17. No direct adverse effects on male fertility was observed at doses up to 1.0 mg/kg/day, a high dose yielding an estimated systemic exposure 11-times the human exposure at the MRHD, based on plasma AUC. In female rats, an increase in early embryonic deaths occurred at 1.0 mg/kg/day. Reduced body weight gain and food consumption were observed in females at the 1.0 mg/kg/day dose.

14 CLINICAL STUDIES

14.1 Glycemic Control Trials in Adults with Type 2 Diabetes Mellitus
In glycemic control trials, VICTOZA® has been studied as monotherapy and in combination with one or two oral anti-diabetic medications or basal insulin. VICTOZA® was also studied in a cardiovascular outcomes trial (LEADER trial). In each of the placebo controlled trials, treatment with VICTOZA® produced clinically and statistically significant improvements in hemoglobin A\textsubscript{1c} and fasting plasma glucose (FPG) compared to placebo. All VICTOZA\textsuperscript{®}-treated patients started at 0.6 mg/day. The dose was increased in weekly intervals by 0.6 mg to reach 1.2 mg or 1.8 mg for patients randomized to these higher doses. VICTOZA® 0.6 mg is not effective for glycemic control and is intended only as a starting dose to reduce gastrointestinal intolerance. See Dosage and Administration (2).

Monotherapy
In this 52-week trial, 746 patients were randomized to VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, or glimepiride 8 mg. Patients who were randomized to glimepiride were initially treated with 2 mg daily for two weeks, increasing to 4 mg daily for another two weeks, and finally increasing to 8 mg daily. Treatment with VICTOZA® 1.8 mg and 1.2 mg resulted in a statistically significant reduction in HbA\textsubscript{1c} compared to glimepiride (Table 3). The percentage of patients who discontinued due to ineffective therapy was 3.6% in the VICTOZA® 1.8 mg treatment group, 6.0% in the VICTOZA® 1.2 mg treatment group, and 10.1% in the glimepiride-treatment group.

The mean age of participants was 53 years, and the mean duration of diabetes was 5 years. Participants were 49.7% male, 77.5% White, 12.6% Black or African American and 35.0% of Hispanic ethnicity. The mean BMI was 33.1 kg/m\textsuperscript{2}.

Table 3 Results of a 52-week monotherapy trial

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Intent-to-Treat Population (N)</th>
<th>HbA\textsubscript{1c} (%) (Mean)</th>
<th>P value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>VICTOZA® 1.2 mg</td>
<td>246</td>
<td>8.2</td>
<td>-0.3*</td>
</tr>
<tr>
<td>VICTOZA® 1.8 mg</td>
<td>251</td>
<td>8.2</td>
<td>-0.5**</td>
</tr>
<tr>
<td>Glimepiride 8 mg</td>
<td>248</td>
<td>8.2</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change from baseline (adjusted mean)</th>
<th>95% CI</th>
<th>P value vs Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.1</td>
<td>(-2.9, -0.3)</td>
<td></td>
</tr>
<tr>
<td>Difference from glimepiride arm (adjusted mean)</td>
<td>-0.6**</td>
<td>(-1.0, -0.1)</td>
<td></td>
</tr>
</tbody>
</table>

*P-value < 0.05
**P-value < 0.0001

Figure 3 Mean HbA\textsubscript{1c} for patients who completed the 52-week trial and for the Last Observation Carried Forward (LOCF, intent-to-treat) data at Week 52 (Monotherapy)

Combination Therapy
Add-on to Metformin
In this 26-week trial, 1091 patients were randomized to VICTOZA® 0.6 mg, VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, placebo, or glimepiride 4 mg (one-half of the maximal approved dose in the United States), all as add-on to metformin. Randomization occurred after a 6-week run-in period consisting of a 3-week initial forced metformin titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin were increased up to 2000 mg/day. Treatment with VICTOZA® 1.2 mg and 1.8 mg as add-on to metformin resulted in a significant mean HbA\textsubscript{1c} reduction relative to placebo add-on to metformin and resulted in a similar mean HbA\textsubscript{1c} reduction relative to glimepiride 4 mg add-on to metformin (Table 4). The percentage of patients who discontinued due to ineffective therapy was 5.4% in the VICTOZA® 1.8 mg + metformin treatment group, 3.3% in the
VICTOZA® 1.2 mg + metformin treatment group, 23.8% in the placebo + metformin treatment group, and 3.7% in the glimepiride + metformin treated group.

The mean age of participants was 57 years, and the mean duration of diabetes was 6 years. Participants were 52.9% male, 86.8% White, 7.2% Black or African American and 16.2% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA₁c from baseline to Week 26. Treatment with VICTOZA® 1.2 mg and VICTOZA® 1.8 mg resulted in statistically significant reductions in HbA₁c relative to sitagliptin 100 mg (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the VICTOZA® 1.2 mg group, 0.5% in the VICTOZA® 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group. From a mean baseline body weight of 94 kg, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy.

Table 5 Results of a 26-week open-label trial of VICTOZA® Compared to Sitagliptin

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Change from baseline (adjusted mean)</th>
<th>Difference from sitagliptin arm (LS mean)</th>
<th>Percentage of patients achieving HbA₁c&lt;7%</th>
<th>Fasting Plasma Glucose (mg/dL) (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) (Mean)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>-1.3</td>
<td>-1.6</td>
<td>-3.5**</td>
<td>83</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.2</td>
<td>-1.1</td>
<td>-2.0</td>
<td>80.0</td>
</tr>
<tr>
<td>Difference from sitagliptin arm (adjusted mean)</td>
<td>-1.3</td>
<td>-1.2</td>
<td>-3.5**</td>
<td>80.0</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA₁c&lt;7%</td>
<td>49</td>
<td>51</td>
<td>50.0</td>
<td></td>
</tr>
</tbody>
</table>

VICTOZA® Compared to Sitagliptin. Both as Add-on to Metformin

In this 26-week, open-label trial, 665 patients on a background of metformin ≥1500 mg per day were randomized to VICTOZA® 1.2 mg once-daily, VICTOZA® 1.8 mg once-daily or sitagliptin 100 mg once-daily, all dosed according to approved labeling. Patients were to continue their current treatment on metformin at a stable, pre- trial dose level and dosing frequency.

The mean age of participants was 56 years, and the mean duration of diabetes was 6 years. Participants were 52.9% male, 86.8% White, 7.2% Black or African American and 16.2% of Hispanic ethnicity. The mean BMI was 32.8 kg/m².

The primary endpoint was the change in HbA₁c from baseline to Week 26. Treatment with VICTOZA® 1.2 mg and VICTOZA® 1.8 mg resulted in statistically significant reductions in HbA₁c relative to sitagliptin 100 mg (Table 5). The percentage of patients who discontinued due to ineffective therapy was 3.1% in the VICTOZA® 1.2 mg group, 0.5% in the VICTOZA® 1.8 mg treatment group, and 4.1% in the sitagliptin 100 mg treatment group. From a mean baseline body weight of 94 kg, there was a mean reduction of 0.3 kg for VICTOZA® 1.2 mg, 3.3 kg for VICTOZA® 1.8 mg, and 0.8 kg for sitagliptin 100 mg.

Table 6 Results of a 26-week open label trial of Insulin detemir as add on to VICTOZA® + metformin compared to continued treatment with VICTOZA® + metformin in patients not achieving HbA₁c<7% after 12 weeks of Metformin and VICTOZA®

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Change from baseline (adjusted mean)</th>
<th>Percentage of patients achieving HbA₁c&lt;7%</th>
<th>Fasting Plasma Glucose (mg/dL) (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) (Mean)</td>
<td>LS mean</td>
<td>95% Confidence Interval</td>
<td>LS mean</td>
</tr>
<tr>
<td>Baseline</td>
<td>-0.9</td>
<td>-0.4</td>
<td>-3.5</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-1.2</td>
<td>-1.1</td>
<td>-3.5**</td>
</tr>
<tr>
<td>Difference from VICTOZA® + metformin arm (LS mean)</td>
<td>-1.2</td>
<td>-1.1</td>
<td>-3.5**</td>
</tr>
</tbody>
</table>

VICTOZA® (liraglutide) injection 1.2 mg, 1.8 mg

VICTOZA® 1.2 mg + Metformin Placebo + Metformin Sitagliptin 100 mg

<table>
<thead>
<tr>
<th>Intent-to-Treat Population (N)</th>
<th>218</th>
<th>221</th>
<th>219</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%) (Mean)</td>
<td>8.4</td>
<td>8.4</td>
<td>8.5</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.5</td>
<td>-0.9</td>
<td>-0.7**</td>
</tr>
<tr>
<td>Change from baseline (adjusted mean)</td>
<td>-0.7**</td>
<td>-0.3**</td>
<td>-0.9</td>
</tr>
<tr>
<td>Difference from sitagliptin arm (adjusted mean)</td>
<td>-0.7**</td>
<td>-0.3**</td>
<td>-0.9</td>
</tr>
<tr>
<td>Percentage of patients achieving HbA₁c&lt;7%</td>
<td>49</td>
<td>51</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Adverse Reactions

This 26-week open-label trial enrolled 665 patients with inadequate glycemic control (HbA₁c 7-10%) on metformin >1500 mg/day alone or inadequate glycemic control (HbA₁c 7.5-8.5%) on metformin >1500 mg/day and a sulfonylurea. Patients who were on metformin and a sulfonylurea discontinued the sulfonylurea then all patients entered a 12-week run-in period during which they received add-on therapy with VICTOZA® titrated to 1.8 mg once-daily. At the end of the run-in period, 498 patients (50%) achieved HbA₁c<7% with VICTOZA® 1.8 mg and metformin and continued treatment in a non-randomized, observational arm. Another 167 patients (17%) withdrew from the trial during the run-in period with approximately one-half of these patients doing so because of gastrointestinal adverse reactions (see Adverse Reactions (6.1)). The 323 patients with HbA₁c <7% (33% of those who entered the run-in period) were randomized to 26 weeks of once-daily insulin detemir administered in the evening as add-on therapy (N=162) or to continued, unchanged treatment with VICTOZA® 1.8 mg and metformin (N=161). The starting dose of insulin detemir was 10 units/day and the mean dose at the end of the 26-week randomized period was 39 units/day. During the 26-week randomized treatment period, the percentage of patients who discontinued due to ineffective therapy was 11.2% in the group randomized to continued treatment with VICTOZA® 1.8 mg and metformin and 12.1% in the group randomized to add-on therapy with insulin detemir.

The mean age of participants was 57 years, and the mean duration of diabetes was 6 years. Participants were 55.7% male, 91.3% White, 5.6% Black or African American and 12.5% of Hispanic ethnicity. The mean BMI was 34.0 kg/m².

Treatment with insulin detemir as add-on to VICTOZA® 1.8 mg + metformin resulted in statistically significant reductions in HbA₁c, and FPG compared to continued, unchanged treatment with VICTOZA® 1.8 mg + metformin alone (Table 6). From a mean baseline body weight of 56 kg after randomization, there was a mean reduction of 0.3 kg in the patients who received insulin detemir add-on therapy compared to a mean reduction of 1.1 kg in the patients who continued on unchanged treatment with VICTOZA® 1.8 mg + metformin alone.

Adverse Reactions

In this 26-week trial, 1041 patients were randomized to VICTOZA® 0.6 mg, VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to glimepiride. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-glimepiride titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of glimepiride were increased to 4 mg/day. The doses of glimepiride could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 56 years, and the mean duration of diabetes was 5 years. Participants were 49.4% male, 64.4% White and 2.8% Black or African American. The mean BMI was 31.3 kg/m².

Treatment with VICTOZA® 1.2 mg and 1.8 mg as add-on to glimepiride resulted in a statistically significant reduction in mean HbA₁c, compared to placebo add-on to glimepiride (Table 7). The percentage of patients who discontinued due to ineffective therapy was 3.0% in the VICTOZA® 1.8 mg + glimepiride treatment group, 3.5% in the VICTOZA® 1.2 mg + glimepiride treatment group, 17.5% in the placebo + glimepiride treatment group, and 6.9% in the rosiglitazone + glimepiride treatment group.

Add-on to Sitagliptin

In this 26-week trial, 1041 patients were randomized to VICTOZA® 0.6 mg, VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, placebo, or rosiglitazone 4 mg (one-half of the maximal approved dose in the United States), all as add-on to sitagliptin. Randomization occurred after a 4-week run-in period consisting of an initial, 2-week, forced-sitagliptin titration period followed by a maintenance period of another 2 weeks. During the titration period, doses of sitagliptin were increased to 4 mg/day. The doses of sitagliptin could be reduced (at the discretion of the investigator) from 4 mg/day to 3 mg/day or 2 mg/day (minimum) after randomization, in the event of unacceptable hypoglycemia or other adverse events.

The mean age of participants was 56 years, and the mean duration of diabetes was 5 years. Participants were 49.4% male, 64.4% White and 2.8% Black or African American. The mean BMI was 31.3 kg/m².
Table 7 Results of a 26-week trial of VICTOZA® as add-on to sulfonylurea

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg + Glimepiride</th>
<th>VICTOZA® 1.2 mg + Glimepiride</th>
<th>Placebo + Glimepiride</th>
<th>Rosiglitazone 4 mg + Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treatment Population (N)</td>
<td>234</td>
<td>228</td>
<td>114</td>
</tr>
</tbody>
</table>

HbA1c (%) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^a\)
- Difference from placebo + glimepiride arm (adjusted mean)\(^a\)
95% Confidence Interval

Percentage of patients achieving HbA1c <7%

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + glimepiride arm (adjusted mean)\(^b\)
95% Confidence Interval

Body Weight (kg) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + glimepiride arm (adjusted mean)\(^b\)
95% Confidence Interval

\(^a\)Least squares mean adjusted for baseline value

\(^b\)Least squares mean adjusted for baseline value

Table 8 Results of a 26-week trial of VICTOZA® as add-on to metformin and sulfonylurea

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg + Metformin + Glimepiride</th>
<th>Placebo + Metformin + Glimepiride</th>
<th>Insulin glargine(^1) + Metformin + Glimepiride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treatment Population (N)</td>
<td>230</td>
<td>174</td>
</tr>
</tbody>
</table>

HbA1c (%) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^a\)
- Difference from placebo + metformin + glimepiride arm (adjusted mean)\(^a\)
95% Confidence Interval

Percentage of patients achieving HbA1c <7%

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + metformin + glimepiride arm (adjusted mean)\(^b\)
95% Confidence Interval

Body Weight (kg) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + metformin + glimepiride arm (adjusted mean)\(^b\)
95% Confidence Interval

\(^a\)Least squares mean adjusted for baseline value

\(^b\)Least squares mean adjusted for baseline value

Table 9 Results of a 26-week open-label trial of VICTOZA® versus Exenatide (both in combination with metformin and/or sulfonylurea)

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg once daily + metformin and/or sulfonylurea</th>
<th>Exenatide 10 mcg twice daily + metformin and/or sulfonylurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treatment Population (N)</td>
<td>233</td>
</tr>
</tbody>
</table>

HbA1c (%) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^a\)
- Difference from exenatide arm (adjusted mean)\(^a\)
95% Confidence Interval

Percentage of patients achieving HbA1c <7%

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from exenatide arm (adjusted mean)\(^b\)
95% Confidence Interval

Body Weight (kg) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from exenatide arm (adjusted mean)\(^b\)
95% Confidence Interval

\(^a\)Least squares mean adjusted for baseline value

\(^b\)Least squares mean adjusted for baseline value

Table 10 Results of a 26-week trial of VICTOZA® as add-on to metformin and thiazolidinedione

<table>
<thead>
<tr>
<th>VICTOZA® 1.8 mg + Metformin + Rosiglitazone</th>
<th>VICTOZA® 1.2 mg + Metformin + Rosiglitazone</th>
<th>Placebo + Metformin + Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intent-to-Treatment Population (N)</td>
<td>178</td>
<td>177</td>
</tr>
</tbody>
</table>

HbA1c (%) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^a\)
- Difference from placebo + metformin + rosiglitazone arm (adjusted mean)\(^a\)
95% Confidence Interval

Percentage of patients achieving HbA1c <7%

Fasting Plasma Glucose (mg/dL) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + metformin + rosiglitazone arm (adjusted mean)\(^b\)
95% Confidence Interval

Body Weight (kg) (Mean)

Baseline
- Change from baseline (adjusted mean)\(^b\)
- Difference from placebo + metformin + rosiglitazone arm (adjusted mean)\(^b\)
95% Confidence Interval

\(^a\)Least squares mean adjusted for baseline value

\(^b\)Least squares mean adjusted for baseline value

\(^c\)For insulin glargine, optimal titration regimen was not achieved for 80% of patients

\(^*\)p-value <0.0001

\(^**\)p-value <0.0001

In this 26-week trial, 581 patients were randomized to VICTOZA® 1.8 mg, placebo, or insulin glargine, all as add-on to metformin and glimepiride. Randomization took place after a 6-week run-in period consisting of a 3-week forced metformin and glimepiride titration period followed by a maintenance period of another 3 weeks. During the titration period, doses of metformin and glimepiride were to be increased up to 2000 mg/day and 4 mg/day, respectively. After randomization, patients randomized to VICTOZA® 1.8 mg underwent a 2 week period of titration with VICTOZA®. During the trial, the VICTOZA® and metformin doses were fixed, although glimepiride and insulin glargine doses could be adjusted. Patients titrated glargine twice-weekly during the first 8 weeks of treatment based on self-measured fasting plasma glucose on the day of titration. After Week 8, the frequency of insulin glargine titration was left to the discretion of the investigator, but, at a minimum, the glargine dose was to be revised, if necessary, at Weeks 12 and 18. Only 20% of glargine-treated patients achieved the pre-specified target fasting plasma glucose of <100 mg/dL. Therefore, optimal titration of the insulin glargine dose was not achieved in most patients.

The mean age of participants was 58 years, and the mean duration of diabetes was 9 years. Participants were 56.5% male, 75.0% White, and 36.6% Black or African American. The mean BMI was 30.5 kg/m².

Treatement with VICTOZA® as add-on to glimepiride and metformin resulted in a statistically significant mean reduction in HbA1c compared to placebo add-on to glimepiride and metformin (Table 8). The percentage of patients who discontinued due to ineffective therapy was 0.9% in the VICTOZA® 1.8 mg + metformin + glimepiride treatment group, 0.4% in the insulin glargine + metformin + glimepiride treatment group, and 11.3% in the placebo + metformin + glimepiride treatment group.

The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 51.9% male, 91.6% White, 5.4% Black or African American and 12.3% of Hispanic ethnicity. The mean BMI was 32.9 kg/m².

Treatement with VICTOZA® as add-on to rosiglitazone and metformin produced a statistically significant reduction in HbA1c compared to placebo add-on to metformin and rosiglitazone (Table 8). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the VICTOZA® 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the VICTOZA® 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.

In this 26-week trial, 533 patients were randomized to VICTOZA® 1.2 mg, VICTOZA® 1.8 mg, or placebo, all as add-on to rosiglitazone (8 mg) plus metformin (2000 mg). Patients underwent a 9 week run-in period (3-week forced dose escalation followed by a 6-week dose maintenance phase) with rosiglitazone (starting at 4 mg and increasing to 8 mg/day within 2 weeks) and metformin (starting at 500 mg with increasing weekly increments of 500 mg to a final dose of 2000 mg/day). Only patients who tolerated the final dose of rosiglitazone (8 mg/day) and metformin (2000 mg/day) and completed the 6-week dose maintenance phase were eligible for randomization into the trial.

The mean age of participants was 55 years, and the mean duration of diabetes was 9 years. Participants were 51.6% male, 84.2% White, 10.2% Black or African American and 16.4% of Hispanic ethnicity. The mean BMI was 33.9 kg/m².

Treatement with VICTOZA® as add-on to rosiglitazone and metformin produced a statistically significant reduction in mean HbA1c compared to placebo add-on to metformin and rosiglitazone (Table 10). The percentage of patients who discontinued due to ineffective therapy was 1.7% in the VICTOZA® 1.8 mg + metformin + rosiglitazone treatment group, 1.7% in the VICTOZA® 1.2 mg + metformin + rosiglitazone treatment group, and 16.4% in the placebo + metformin + rosiglitazone treatment group.
In this 26-week, double-blind, randomized, placebo-controlled, parallel-group trial, 279 patients with moderate renal impairment, as per MDRD formula (eGFR 30–59 mL/min/1.73 m²), were randomized to VICTOZA® or placebo once daily. VICTOZA® was added to the patient’s stable pre-trial antidiabetic regimen (insulin therapy and/or metformin, pioglitazone, or sulfonylurea). The dose of VICTOZA® was escalated according to approved labeling to achieve a dose of 1.8 mg per day. The insulin dose was reduced by 20% at randomization for patients with baseline HbA₁c ≥ 8% and fixed until liraglutide dose escalation was complete. Dose reduction of insulin and SU was allowed in case of hypoglycemia; up titration of insulin was allowed but not beyond the pre-trial dose.

The mean age of participants was 67 years, and the mean duration of diabetes was 15 years. Participants were 50.5% male, 92.3% White, 6.6% Black or African American, and 7.2% of Hispanic ethnicity. The mean BMI was 33.9 kg/m². Approximately half of patients had an eGFR between 30 and <45 mL/min/1.73 m².

Treatment with VICTOZA® resulted in a statistically significant reduction in HbA₁c from baseline at Week 26 compared to placebo (see Table 11). 123 patients reached the 1.8 mg dose of VICTOZA®.

### Table 11 Results of a 26-week trial of VICTOZA® compared to placebo in Patients with Renal Impairment

<table>
<thead>
<tr>
<th>Intent to Treat Population (N)</th>
<th>VICTOZA® 1.8 mg + insulin and/or OAD</th>
<th>Placebo + insulin and/or OAD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA₁c (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>8.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Change from baseline (estimated mean)</td>
<td>-0.9</td>
<td>-0.4</td>
</tr>
<tr>
<td>Difference from placebo (95% Confidence Interval)</td>
<td>-0.6 (-0.8, -0.3)</td>
<td></td>
</tr>
<tr>
<td>Proportion achieving HbA₁c &lt; 7%</td>
<td>39.3%</td>
<td>19.7</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline (mean)</td>
<td>171</td>
<td>157</td>
</tr>
<tr>
<td>Change from baseline (estimated mean)</td>
<td>-22</td>
<td>-10</td>
</tr>
<tr>
<td>Difference from placebo (95% Confidence Interval)</td>
<td>-12 (-23, -0.8)</td>
<td></td>
</tr>
</tbody>
</table>

*Intention-to-treatment study

*Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit. Multiple imputation method modeled "wash out" of the treatment effect for patients having missing data who discontinued treatment.

*Early treatment discontinuation, before week 26, occurred in 25% and 22% of VICTOZA® and placebo patients, respectively.

Based on the known number of subjects achieving HbA₁c < 7%. When applying the multiple imputation method described in b) above, the estimated percents achieving HbA₁c < 7% are 47.6% and 24.9% for VICTOZA® and placebo, respectively.

*Estimated using a mixed model for repeated measurement with treatment, country, stratification groups as factors and baseline as a covariate, all nested within visit.

<table>
<thead>
<tr>
<th>*p-value &lt;0.001</th>
</tr>
</thead>
</table>

### 14.2 Glycemic Control Trial in Pediatric Patients 10 Years of Age and Older with Type 2 Diabetes Mellitus

VICTOZA® was evaluated in a 26-week, double-blind, randomized, parallel group, placebo-controlled multi-center trial (NCT01541215), in 134 pediatric patients with type 2 diabetes aged 10 years and older. Patients were randomized to VICTOZA® once-daily or placebo once-daily in combination with metformin with or without basal insulin treatment. All patients were on a metformin dose of 1000 to 1500 mg/day prior to randomization. The basal insulin dose was decreased by 20% at randomization and VICTOZA® was titrated weekly by 0.6 mg for 2 to 3 weeks based on tolerability and an average fasting plasma glucose goal of ≤110 mg/dL.

The mean age was 14.6 years; 29.9% were ages 10-14 years, and 70.1% were greater than 14 years of age. 38.1% were male, 64.9% were White, 13.4% were Asian, 11.9% were Black or African American; 29.1% were of Hispanic or Latino ethnicity. The mean BMI was 33.9 kg/m². A history of previous myocardial infarction was reported in 31% of randomized individuals, a prior revascularization procedure in 39%, a prior ischemic stroke in 11%, documented symptomatic coronary disease in 9%, documented asymptomatic cardiac ischemia in 26%, and a diagnosis of New York Heart Association (NYHA) class II or III heart failure in 14%. The mean eGFR at baseline was 79 mL/min/1.73 m² and 41.8% of patients had mild renal impairment (eGFR 60 to 90 mL/min/1.73 m²) or 20.7% had moderate renal impairment (eGFR 30 to 60 mL/min/1.73 m²) and 2.4% of patients had severe renal impairment (eGFR <30 mL/min/1.73 m²).

At baseline, patients treated their diabetes with; diet and exercise only (3.9%), oral antidiabetic drugs only (51.5%), oral antidiabetic drugs and insulin (36.7%) or insulin only (7.9%). The most common background antidiabetic drugs used at baseline and in the trial were metformin, sulfonylurea and insulin. Use of DPP-4 inhibitors and other GLP-1 receptor agonists was excluded by protocol and SGLT-2 inhibitors were either not approved or not widely available. At baseline, cardiovascular disease and risk factors were managed with; non-diuretic antihypertensives (92.4%), diuretics (41.8%), statin therapy (72.1%) and platelet aggregation inhibitors (66.8%). During the trial, investigators could modify anti-diabetic and cardiovascular medications to achieve local standard of care treatment targets with respect to blood glucose, lipid, and blood pressure, and manage patients recovering from an acute coronary syndrome or stroke event per local treatment guidelines.

For the primary analysis, a Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferiority was demonstrated. Type 1 error was controlled across multiple tests.

For the primary analysis, A Cox proportional hazards model was used to test for non-inferiority against the pre-specified risk margin of 1.3 for the hazard ratio of MACE and to test for superiority on MACE if non-inferiority was demonstrated. Type 1 error was controlled across multiple tests.

VICTOZA® significantly reduced the occurrence of MACE. The estimated hazard ratio (95% Cl) for time to first MACE was 0.87 (0.78, 0.97). Refer to Figure 5 and Table 13.

Vital status was available for 99.7% of subjects in the trial. A total of 828 deaths were recorded during the LEADER trial. A majority of the deaths in the trial were categorized as cardiovascular deaths and non-cardiovascular deaths were balanced between the treatment groups (3.5% in patients treated with VICTOZA® and 3.6% in patients treated with placebo). The estimated hazard ratio of time to all-cause death for VICTOZA® compared to placebo was 0.85 (0.74, 0.97).
Hypersensitivity Reactions
Inform patients that serious hypersensitivity reactions have been reported during postmarketing use of VICTOZA®. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking VICTOZA® and seek medical advice promptly if such symptoms occur (see Warnings and Precautions (5.6)).

Jaundice and Hepatitis
Inform patients that jaundice and hepatitis have been reported during postmarketing use of liraglutide. Instruct patients to contact their physician if they develop jaundice.

Instructions
Advise patients that the most common side effects of VICTOZA® are headache, nausea and diarrhea. Nausea is most common when first starting VICTOZA®, but decreases over time in the majority of patients and does not typically require discontinuation of VICTOZA®.

Inform patients not to take an extra dose of VICTOZA® to make up for a missed dose. If a dose is missed, the once-daily regimen should be resumed as prescribed with the next scheduled dose. If more than 3 days have elapsed since the last dose, advise the patient to reinitiate VICTOZA® at 0.6 mg to mitigate any gastrointestinal symptoms associated with reinitiation of treatment. VICTOZA® should be titrated at the discretion of the prescribing physician (see Dosage and Administration (2)).

Dehydration and Renal Failure
Advise patients treated with VICTOZA® of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

Risk of Thyroid C-cell Tumors
Inform patients that liraglutide causes benign and malignant thyroid C-cell tumors in mice and rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, hoarseness, dysphagia, or dyspnea) to their physician (see Boxed Warning and Warnings and Precautions (5.1)).

Dehydration and Renal Failure
Advise patients treated with VICTOZA® of the potential risk of dehydration due to gastrointestinal adverse reactions and to take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function, which in some cases may require dialysis.

Pancreatitis
Inform patients of the potential risk for pancreatitis. Explain that persistent severe abdominal pain that may radiate to the back and which may or may not be accompanied by vomiting, is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue VICTOZA® promptly and contact their physician if persistent severe abdominal pain occurs (see Warnings and Precautions (5.2)).

Acute Gallbladder Disease
Inform patients of the potential risk for cholecystitis or cholelithiasis. Instruct patients to contact their physician if cholecystitis or cholelithiasis is suspected for appropriate clinical follow-up.

Never Share a VICTOZA® Pen Between Patients
Advise patients that they must never share a VICTOZA® pen with another person, even if the needle is changed, because doing so carries a risk for transmission of blood-borne pathogens.

Hypoglycemia
Inform patients that hypoglycemia has been reported when VICTOZA® is used with insulin secretagogues or insulin and may occur in pediatric patients regardless of concomitant anti diabetic treatment. Educate patients or caregivers on the signs and symptoms of hypoglycemia.

VICTOZA® (liraglutide) injection 1.2 mg, 1.8 mg pen NDC 0169-4060-13

Table 13  Treatment Effect for the Primary Composite Endpoint, MACE, and its Components in the LEADER Trial (Patients with T2DM and Atherosclerotic CVD)a

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo N=4672</th>
<th>VICTOZA® N=4688</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke (MACE) (time to first occurrence)</td>
<td>608 (13.0%)</td>
<td>694 (14.9%)</td>
<td>0.87 (0.78, 0.97)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarctionb</td>
<td>281 (6.0%)</td>
<td>317 (6.8%)</td>
<td>0.88 (0.75, 1.03)</td>
</tr>
<tr>
<td>Non-fatal strokeb</td>
<td>159 (3.4%)</td>
<td>177 (3.8%)</td>
<td>0.89 (0.72, 1.11)</td>
</tr>
<tr>
<td>Cardiovascular deathc</td>
<td>219 (4.7%)</td>
<td>278 (6%)</td>
<td>0.78 (0.60, 0.99)</td>
</tr>
</tbody>
</table>

aFull analysis set (all randomized patients)
bCox-proportional hazards model with treatment as a factor
p-value for superiority (2-sided) 0.011
Number and percentage of first events

16  HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied
VICTOZA® Injection: 18 mg/3 mL (6 mg/mL) clear, colorless solution in a pre-filled, single-patient-use pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg is available in the following package sizes:

2 x VICTOZA® pen                NDC 0169-4060-12
3 x VICTOZA® pen                NDC 0169-4060-13

16.2 Recommended Storage
Prior to first use, VICTOZA® should be stored in a refrigerator between 36°F to 46°F (2°C to 8°C). Do not store in the freezer or directly adjacent to the refrigerator cooling element. Do not freeze VICTOZA® and do not use VICTOZA® if it has been frozen.

After first use of the VICTOZA® pen, the pen can be stored for 30 days at controlled room temperature (59°F to 86°F; 15°C to 30°C) or in a refrigerator (36°F to 46°F; 2°C to 8°C). Keep the pen cap on when not in use. Protect VICTOZA® from excessive heat and sunlight. Always remove and safely discard the needle after each injection and store the VICTOZA® pen without an injection needle attached. This will reduce the potential for contamination, infection, and leakage while also ensuring dosing accuracy. Always use a new needle for each injection to prevent contamination.

17  PATIENT COUNSELING INFORMATION
Advise the patient to read the FDA-approved patient labeling (Medication Guide).

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Version: 14
VICTOZA® is a registered trademark of Novo Nordisk A/S.

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1-877-484-2869
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US21VZ00069 12/2021
Medication Guide

VICTOZA® (VIC-tow-za) (liraglutide) injection, for subcutaneous use

Read this Medication Guide before you start using VICTOZA® and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about VICTOZA®?

VICTOZA® may cause serious side effects, including:

• Possible thyroid tumors, including cancer. Tell your healthcare provider if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer. In studies with rats and mice, VICTOZA® and medicines that work like VICTOZA® caused thyroid tumors, including thyroid cancer. It is not known if VICTOZA® will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinomas (MTC) in people.

• Do not use VICTOZA® if you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC), or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

What is VICTOZA®?

VICTOZA® is an injectable prescription medicine used:

• along with diet and exercise to lower blood sugar (glucose) in adults and children who are 10 years of age and older with type 2 diabetes mellitus.

• to reduce the risk of major cardiovascular events such as heart attack, stroke or death in adults with type 2 diabetes mellitus with known heart disease.

VICTOZA® is not for use in people with type 1 diabetes. It should not be used with other medicines that contain liraglutide. It is not known if VICTOZA® is safe and effective to lower blood sugar (glucose) in children under 10 years of age.

Who should not use VICTOZA®?

Do not use VICTOZA® if:

• you or any of your family have ever had a type of thyroid cancer called medullary thyroid carcinoma (MTC) or if you have an endocrine system condition called Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

• you are allergic to liraglutide or any of the ingredients in VICTOZA®. See the end of this Medication Guide for a complete list of ingredients in VICTOZA®.

What should I tell my healthcare provider before using VICTOZA®?

Before using VICTOZA®, tell your healthcare provider if you have any other medical conditions, including if you:

• have or have had problems with your pancreas, kidneys, or liver.

• have severe problems with your stomach, such as slowed emptying of your stomach (gastroparesis) or problems with digesting food.

• are pregnant or plan to become pregnant. It is not known if VICTOZA® will harm your unborn baby. Tell your healthcare provider if you become pregnant while using VICTOZA®.

• are breastfeeding or plan to breastfeed. It is not known if VICTOZA® passes into your breast milk. You should talk with your healthcare provider about the best way to feed your baby while using VICTOZA®.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VICTOZA® may affect the way these medicines work and some medicines may affect the way VICTOZA® works.

Before using VICTOZA®, talk to your healthcare provider about low blood sugar and how to manage it. Tell your healthcare provider if you are taking other medicines to treat diabetes, including insulin or sulfonylureas.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I use VICTOZA®?

• Read the Instructions for Use that comes with VICTOZA®.

• Use VICTOZA® exactly as your healthcare provider tells you to.

• Your healthcare provider should show you how to use VICTOZA® before you use it for the first time.

• Use VICTOZA® 1 time each day, at any time of the day.

• VICTOZA® may be taken with or without food.

• VICTOZA® is injected under the skin (subcutaneously) of your stomach (abdomen), thigh, or upper arm. Do not inject VICTOZA® into a muscle (intramuscularly) or vein (intravenously).

• Do not mix insulin and VICTOZA® together in the same injection.

• You may give an injection of VICTOZA® and insulin in the same body area (such as your stomach area), but not right next to each other.

• If you miss a dose of VICTOZA®, take the missed dose at the next scheduled dose. Do not take 2 doses of VICTOZA® at the same time.

• If you take too much VICTOZA®, call your healthcare provider right away. Taking too much VICTOZA® may cause severe nausea, severe vomiting, and low blood sugar (hypoglycemia).

• Change (rotate) your injection site with each injection. Do not use the same site for each injection.

• Do not share your VICTOZA® pen with other people, even if the needle has been changed.

• You may give other people a serious infection, or get a serious infection from them.

• The VICTOZA® pen you are using should be thrown away 30 days after you start using it.

Your dose of VICTOZA® and other diabetes medicines may need to change because of:

• change in level of physical activity or exercise, weight gain or loss, increased stress, illness, change in diet, or because of other medicines you take.

What are the possible side effects of VICTOZA®?

VICTOZA® may cause serious side effects, including:

• See “What is the most important information I should know about VICTOZA®?”

• inflammation of your pancreas (pancreatitis). Stop using VICTOZA® and call your healthcare provider right away if you have severe pain in your stomach area (abdomen) that will not go away, with or without vomiting. You may feel the pain from your abdomen to your back.

• low blood sugar (hypoglycemia). Your risk for getting low blood sugar may be higher if you use VICTOZA® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin.

In children who are 10 years of age and older, the risk for low blood sugar may be higher with VICTOZA® regardless of use with another medicine that can also lower blood sugar.

Signs and symptoms of low blood sugar may include:

• dizziness or light-headedness
• blurred vision
• anxiety, irritability, or mood changes
• slurred speech
• confusion or drowsiness
• shakiness
• weakness
• headache
• fast heartbeat
• feeling jittery
• kidney problems (kidney failure). In people who have kidney problems, diabetes, nausea, and vomiting may cause a loss of fluids (dehydration) which may cause kidney problems to get worse.

• serious allergic reactions. Stop using VICTOZA® and get medical help right away, if you have any symptoms of a serious allergic reaction including:

  • swelling of your face, lips, tongue or throat
  • itching, rash, hives, or skin thickening
  • severe or life-threatening allergies

  • problems breathing or swallowing
  • severe rash or itching
  • very rapid heartbeat

• gallbladder problems. Gallbladder problems have happened in some people who take VICTOZA®.

  • pain in the right side or middle upper stomach area
  • nausea and vomiting
  • fever
  • your skin or the white part of your eyes turns yellow

The most common side effects of VICTOZA® may include:

• nausea, diarrhea, vomiting, decreased appetite, indigestion and constipation.

Talk to your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of VICTOZA®.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of VICTOZA®.

Medicines are sometimes prescribed for purposes other than those listed in this Medication Guide. Do not use VICTOZA® for a condition for which it was not prescribed. Do not give VICTOZA® to other people, even if they have the same symptoms that you have. It may harm them. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about VICTOZA® that is written for health professionals.

What are the ingredients in VICTOZA®?

Active Ingredient: Liraglutide

Inactive Ingredients: Disodium phosphate dihydrate, propylene glycol, phenol and water for injection
Instructions for Use

Victoza® (liraglutide) injection

Needle (example)

Outer needle cap
Inner needle cap
Needle
Protective tab

Victoza® Pen
Pen cap
Rubber stopper
Cartridge Tip
Cartridge scale
Dose Display
Pointer
Dose button
Flow check symbol

If you are having problems using your Victoza® pen, call toll free 1-877-484-2869 or visit victoza.com.

First read the Medication Guide that comes with your Victoza® single-patient-use pen and then read this Patient Instructions for Use for information about how to use your Victoza® pen the right way. These instructions do not take the place of talking with your healthcare provider about your medical condition or your treatment.

Do not share your Victoza® Pen with other people, even if the needle has been changed. You may give other people a serious infection, or get a serious infection from them. Your Victoza® pen is a disposable single-patient-use prefilled pen injector that contains 3 mL of Victoza® and will deliver doses of 0.6 mg, 1.2 mg or 1.8 mg. The number of doses that you can take with a Victoza® pen depends on the dose of medicine that is prescribed for you. Your healthcare provider will tell you how much Victoza® to take. Victoza® pen should be used with Novo Nordisk disposable needles. Talk to your healthcare provider or pharmacist for more information about needles for your Victoza® pen.

Important Information

△ Always use a new needle for each injection to prevent contamination.
△ Always remove the needle after each injection, and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage of liraglutide, blocked needles and inaccurate dosing.
△ Keep your Victoza® pen and all medicines out of the reach of children.
△ If you drop your Victoza® pen, repeat “First Time Use For Each New Pen” (steps A through D).
△ Be careful not to bend or damage the needle.
△ Do not use the cartridge scale to measure how much Victoza® to inject.
△ Be careful when handling used needles to avoid needle stick injuries.
△ You can use your Victoza® pen for up to 30 days after you use it the first time.

First Time Use for Each New Pen

Step A. Check the Pen

• Take your new Victoza® pen out of the refrigerator.
• Wash hands with soap and water before use.
• Check pen label before each use to make sure it is your Victoza® pen.
• Pull off pen cap (See Figure A).
• Check Victoza® in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
• Wipe the rubber stopper with an alcohol swab.

Step B. Attach the Needle

• Remove protective tab from outer needle cap (See Figure B).
• Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure.
• Pull off outer needle cap (See Figure C). Do not throw away.
• Pull off inner needle cap and throw away (See Figure D). A small drop of liquid may appear. This is normal.

Step C. Dial to the Flow Check Symbol

This step is done only Once for each new pen and is Only required the first time you use a new pen.

• Turn dose selector until flow check symbol (←) lines up with pointer (See Figure E). The flow check symbol does not administer the dose as prescribed by your healthcare provider.
• To select the dose prescribed by your healthcare provider, continue to Step G under “Routine Use”.

Step D. Prepare the Pen

• Hold pen with needle pointing up.
• Tap cartridge gently with your finger a few times to bring any air bubbles to the top of the cartridge (See Figure F).
• Keep needle pointing up and press dose button until 0 mg lines up with pointer (See Figure G). Repeat steps C and D, up to 6 times, until a drop of Victoza® appears at the needle tip.

If you still see no drop of Victoza®, use a new pen and contact Novo Nordisk at 1-877-484-2869.

Continue to Step G under “Routine Use”.

Routine Use

Step E. Check the Pen

• Take your Victoza® pen from where it is stored.
• Wash hands with soap and water before use.
• Check pen label before each use to make sure it is your Victoza® pen.
• Pull off pen cap (See Figure H).
• Check Victoza® in the cartridge. The liquid should be clear, colorless and free of particles. If not, do not use.
• Wipe the rubber stopper with an alcohol swab.

Step F. Attach the Needle

• Remove protective tab from outer needle cap.
• Push outer needle cap containing the needle straight onto the pen, then screw needle on until secure (See Figure I).
• Pull off outer needle cap. Do not throw away (See Figure J).
• Pull off inner needle cap and throw away (See Figure K). A small drop of liquid may appear. This is normal.

Step G. Dial the Dose

• Victoza® pen can give a dose of 0.6 mg (starting dose), 1.2 mg or 1.8 mg. Be sure that you know the dose of Victoza® that is prescribed for you.
• Turn the dose selector until your needed dose lines up with the pointer (0.6 mg, 1.2 mg or 1.8 mg) (See Figure L). You will hear a “click” every time you turn the dose selector. Do not set the dose by counting the number of clicks you hear.
• If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza® to come out.

Step H. Injecting the Dose

• Insert needle into your skin in the stomach (abdomen), thigh or upper arm. Use the injection technique shown to you by your healthcare provider. Do not inject Victoza® into a vein or muscle.
• Press down on the center of the dose button to inject until 0 mg lines up with the pointer (See Figure M).
• Be careful not to touch the dose display with your other fingers. This may block the injection.
• Keep the dose button pressed down and make sure that you keep the needle under the skin for a full count of 6 seconds to make sure the full dose is injected. Keep your thumb on the injection button until you remove the needle from your skin (See Figure N).
• Change (rotate) your injection sites within the area you choose for each dose. Do not use the same injection site for each injection.

Step I. Withdraw Needle

• You may see a drop of Victoza® at the needle tip. This is normal and it does not affect the dose you just received. If blood appears after you take the needle out of your skin, apply light pressure, but do not rub the area (See Figure O).

Step J. Remove and Dispose of the Needle

• Carefully put the outer needle cap over the needle (See Figure P).
• Be careful not to bend or damage the needle.
• If you select a wrong dose, change it by turning the dose selector backwards or forwards until the correct dose lines up with the pointer. Be careful not to press the dose button when turning the dose selector. This may cause Victoza® to come out.

Caring for your Victoza® pen

• After removing the needle, put the pen cap on your Victoza® pen and store your Victoza® pen without the needle attached (See Figure Q).
• Do not try to refill your Victoza® pen – it is prefilled and is disposable.
• Do not try to repair your pen or pull it apart.
• Keep your Victoza® pen away from dust, dirt and liquids.
• If cleaning is needed, wipe the outside of the pen with a clean, damp cloth.

First, second, and third person.
How should I store Victoza®?

**Before use:**
- Store your new, unused Victoza® pen in the refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- If Victoza® is stored outside of refrigeration (by mistake) prior to first use, it should be used or thrown away within 30 days.
- Do not freeze Victoza® or use Victoza® if it has been frozen. Do not store Victoza® near the refrigerator cooling element.

**Pen in use:**
- Use a Victoza® pen for only 30 days. Throw away a used Victoza® pen 30 days after you start using it, even if some medicine is left in the pen.
- Store your Victoza® pen at 59ºF to 86ºF (15ºC to 30ºC), or in a refrigerator at 36ºF to 46ºF (2ºC to 8ºC).
- When carrying the pen away from home, store the pen at a temperature between 59ºF to 86ºF (15ºC to 30ºC).
- If Victoza® has been exposed to temperatures above 86ºF (30ºC), it should be thrown away.
- Protect your Victoza® pen from heat and sunlight.
- Keep the pen cap on when your Victoza® pen is not in use.
- Always remove the needle after each injection and store your pen without the needle attached. This reduces the risk of contamination, infection, leakage and inaccurate dosing.